

Sarcopenia in women with rheumatoid arthritis

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Abstract

Objective: To assess sarcopenia status in women with rheumatoid arthritis (RA).

Material and Methods: Thirty female patients with RA and 30 female controls without RA were enrolled in this study. Sarcopenia status in patients with RA was evaluated by assessing body composition using dual X-ray absorptiometry (DXA). C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR) were measured, and body mass index (BMI) and Disease Activity Score (DAS28) were calculated. Because sarcopenia differs between men and women, the study groups comprised only females.

Results: It was found that skeletal muscle index (SMI) was lower in patients with RA (5.83 ± 0.807) than in controls (7.30 ± 1.640). Sarcopenia (in females with an SMI of ≤ 5.75 kg/m²) was more common in the RA group and the difference was statistically significant ($p=0.004$). Sarcopenia was more common in patients with RA who were normal or overweight than in those who were obese according to their BMI. There was no relationship between sarcopenia and DAS28 in the RA group ($p=0.530$), whereas CRP levels were significantly higher in patients with sarcopenia ($p=0.230$). No relationship was found between drug use and sarcopenia in the RA group.

Conclusion: It was found that SMI was decreased and sarcopenia risk was elevated in patients with RA and the risk was higher in non-obese patients.

Keywords: Rheumatoid arthritis, sarcopenia, DXA

Introduction

Most patients with rheumatoid arthritis (RA) suffer from muscular weakness (1). Studies evaluating body composition (BC) in RA patients are limited. Evidence has shown that fat-to-lean mass ratio and their distributions have important effects on health status. Decreased lean mass, extreme term "sarcopenia," and increased fat are indicators of poor health in the general population. Loss of lean mass causes weakness, disability, and metabolic abnormalities (2). In most studies, body mass index (BMI), an index that evaluates body weight according to height, has been used as representative of BC. However, as individuals with similar BMI could have a diverse BC, this approach has been questioned (3).

The current definition of sarcopenia includes loss of functional quality in addition to muscle weakness and muscle protein mass loss (4).

Sarcopenia is a syndrome in which muscle mass loss is linked to functional loss. A number of risk factors and mechanisms contribute to sarcopenia development. The most common cause is old age; age-related changes in hormone and cytokine levels are important risk factors. However, energy shortage, lack of physical activity, poor diet, human immunodeficiency virus (HIV) infection, chronic inflammatory diseases (e.g., RA), insulin resistance, type II diabetes mellitus, and impaired tissue repair can lead to sarcopenia in younger individuals (4, 5). The deleterious effects of sarcopenia include a decrease in muscle strength, neuromuscular weakness, and balance disorders due to immobility (6).

It is assumed that sarcopenia is a consequence of hormonal and immunological changes that occur on account of aging. Cytokines, particularly interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α), are believed to increase muscle loss (6). Recent studies have shown that chronic inflammatory diseases lead to sarcopenia (7). It is believed that the inflammatory cytokines TNF- α and interleukin-1 β (IL-1 β) have a pivotal role in RA pathogenesis. Given that TNF- α is elevated in RA, one could propose that RA may cause and accelerate the progression of sarcopenia (8). In patients with RA, a decrease in physical activity (9), elevated TNF- α and IL-1 β levels, increased energy expenditure during rest, high C-reactive protein (CRP) levels, immobility secondary to stiffness, and pain increase the risk of sarcopenia (8).

In present study, fat mass, lean mass, and bone mass were measured by dual X-ray absorptiometry (DXA) in the whole body and body parts (upper limb, lower limb, and trunk); thereby, sarcopenia status was assessed by comparing patients with RA and controls without RA.



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Material and Methods

Study subjects

Thirty female subjects (age: 35-50 years) who were followed in a rheumatology outpatient clinic and diagnosed as having RA according to the 1987 American College of Rheumatology (ACR) classification criteria for RA (10) with at least 2 years disease duration and 30 female patients (age: 35-50 years) with mechanical back pain were enrolled in this study. Written informed consent was obtained from all subjects.

Whole body DXA scan was performed using a DXA scanner (Hologic QDR 4500 W, Waltham, MA). Fat mass, lean mass, and bone mass were measured by DXA in the whole body (except head) and body parts (upper limb, lower limb, and trunk) and analyzed. Automatic measurements of whole BC and total and regional body tissue masses were performed by a technician using a scanner with a software validated by the manufacturer. Daily quality control and calibration procedures were performed according to the manufacturer's instructions. Body weight and height were measured in all subjects using the standard protocols, with the patients in an upright position and dressed lightly without shoes.

Total appendicular muscle mass was calculated by fat- and bone-free tissue detections of upper and lower limbs. Then, skeletal muscle index (SMI) was calculated using the following equation: appendicular skeletal muscle mass (ASM)/height² (11).

According to the criteria recommended by Janssen et al. (12), sarcopenia was defined as a relative SMI of ≤ 5.75 kg/m² in women and ≤ 8.50 kg/m² in men. Because sarcopenia differs between men and women, the study groups consisted of women.

BMI was calculated as body weight (kg)/height (m²) and patients were classified as underweight (<18.5), normal (18.5-24.9), overweight (25-29.9), and obese (>30) as accepted by the National Health Institute (NIH) and World Health Organization (WHO) (13, 14).

Glucocorticoids, non-biological disease-modifying antirheumatic drug (DMARD), and biological agent usage was examined. Moreover, CRP levels and ESR were assessed; thereafter, DAS28 was calculated in patients with RA using their CRP levels.

Nutritional characteristics, physical activity levels, medications, and co-morbid diseases as well as clinical characteristics were determined for each subject. Patients with chronic disorders such as type II diabetes mellitus or other rheu-

matologic diseases were excluded from the study. Those with malnutrition according to the mini nutrition test were also excluded (15).

CRP (mg/L) was assessed automatically by the nephelometric method (Immagine® Immunochemistry Systems, Galway, Ireland Beckman Coulter Inc.) using USE test kits (Galway, Ireland Beckman Coulter Inc.). RF (IU/mL) was assessed automatically by the nephelometric method (Immagine® Immunochemistry Systems, Galway, Ireland, Beckman Coulter Inc.) using USE test kits (Galway, Ireland, Beckman Coulter Inc.). ESR (mm/h) was measured automatically using SEDISystem BD® (MD, USA, Becton Dickinson Inc.). Anti-cyclic citrullinated peptide (CCP) (U/mL) was measured automatically in Triturus® (Princeton, NJ, USA, Inverness Medical) using test kits (Aeskulisa Inc.).

Statistical analysis

Data from the RA and control groups were assessed using the chi-square test, Fisher's exact test, and Mann-Whitney U test. Data in the tables are presented as mean \pm standard deviation (SD). The significance level was set at $p=0.05$ was set as significance level. All data were analyzed by SPSS version 14 (SPSS, Chicago, IL, USA).

Results

The subjects were classified into 2 groups. In first group, there were 30 patients with RA; the

second group comprised 30 control subjects. All subjects were female.

When the subjects in both groups were compared in terms of age, body weight and BMI, no significant difference was found between the groups in terms of age ($p>0.05$), whereas the difference in body weight and BMI was statistically significant ($p<0.05$). Furthermore, CRP levels and ESR were significantly higher in the RA group ($p<0.05$) (Table 1).

When the subjects in both groups were stratified as normal, overweight, or obese according to their BMI, no significant difference was found between the groups ($p>0.05$) (Table 2). When evaluating disease activity in terms of the DAS28 score in the RA group, it was found that 18 patients (60.0%) were in remission, and 2 patients (6.7%) had mild disease activity, 9 (30.0%) had moderate disease activity, and 1 (3.3%) had with severe disease activity. Among the patients with RA, CCP levels were normal in 13 patients (43.3%) and high in 17 patients (56.7%). In the same group, RF levels were found to be normal in 9 patients (30.0%) and high in 21 patients (70.0%). Of the patients with RA, 5 (16.7%) had morning stiffness, whereas 25 (83.3%) did not.

When SMI was compared between the groups, SMI values were significantly lower in the RA group ($p<0.05$) (Table 3).

Table 1. Characteristics of the RA and control groups

	RA (n=30)	Control (n=30)	Outcome
Age	47.70 \pm 5.49	47.70 \pm 5.49	$p=0.962$
Weight (kg)	71.07 \pm 12.44	81.93 \pm 11.93	$p=0.001$
BMI (kg/m ²)	28.79 \pm 5.20	32.62 \pm 4.45	$p=0.003$
CRP	9.87 \pm 12.31	4.31 \pm 3.01	$p=0.022$
ESR (mm/h)	31.00 \pm 27.11	19.46 \pm 12.83	$p=0.040$

RA: rheumatoid arthritis; BMI: body mass index;

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate

Table 2. Comparison of the RA and control group according to BMI

Groups	BMI			Total
	Normal 18.5-24.9	Overweight 25-29.9	Obese 30-39.9	
RA, n (%)	6	11	13	30
	20	36.7	43.3	100
Control, n (%)	1	10	19	30
	3.3	33.3	63.3	100
Total, n (%)	7	21	32	60
	11.7	35.0	53.3	100

RA: rheumatoid arthritis; BMI: body mass index

When the subjects in both group were compared according to sarcopenia status ($SMI \leq 5.75 \text{ kg/m}^2$), it was found that sarcopenia was significantly more common (43.3%) in the RA group (Table 4).

When the patients with RA were stratified as normal, overweight, or obese according to their BMI and then comparison was performed, it was found that sarcopenia was less common in obese patients (7.6%), whereas it was more common in normal and overweight patients (Table 4). Most RA patients with sarcopenia were normal or overweight (92.4%), whereas most RA patients without sarcopenia were obese (70.6%). According to these results, sarcopenia was more common in non-obese RA patients (Table 5).

When CRP levels were evaluated in relation to sarcopenia, RA patients with sarcopenia had significantly higher CRP levels ($p=0.023$) (Table 6). When the relationship between sarcopenia and DAS28 scores was evaluated, no significant difference was found ($p=0.530$).

Table 6 shows medication usage in patients with RA. Sarcopenia was seen in 5 (35.7%) of

14 subjects undergoing steroid therapy, 11 (45.8%) of 24 subjects undergoing DMARD therapy, and 3 (33.3%) of 10 subjects receiving biological agents. According to these results, there was no significant difference between medication usage (steroids, DMARDs, or biological agents) in terms of sarcopenia.

In our study, only female patients with RA were enrolled. Sarcopenia in male patients with RA was not examined. This is a limitation of our study. Furthermore, we did not assess muscle performance in our study.

Discussion

RA is an autoimmune disease with unknown etiology characterized by symmetric synovitis and occasional extra-articular involvement (16). Muscle mass loss occurs in the course of time because of decreased physical activity, increased energy expenditure during rest, and hormonal and immunological alterations seen in patients with RA (9). In RA, loss in body cell mass is more prominent in skeletal muscles, although the effects can also be detected in the immune system and visceral organs (5).

Sarcopenia includes diminished functional quality as well as loss in muscle strength and muscle protein mass. Numerous risk factors contribute to sarcopenia development. The most common cause is old age, which involves alterations in hormone and cytokine levels that are well known as important risk factors. However, energy shortage, lack of physical activity, poor diet, HIV and chronic inflammatory diseases, insulin resistance, type II diabetes mel-

litus, and impaired tissue repair can cause sarcopenia in younger individuals. The proposed underlying mechanisms include alterations in the muscle-protein turnover, remodeling in muscle tissue, loss of α -motor neurons and muscle cell formation, and apoptosis (17, 4, 5).

We sought to evaluate the association between sarcopenia and RA, which is a common chronic inflammatory disease worldwide, because there are few studies in the literature about this issue.

Muscle mass loss is a process that occurs on account of aging. With aging, muscle mass decreases, whereas intra-muscular fat tissue increases. Particularly, these changes occur more prominently in women (18). The number of muscle fibers decreases and there is specific atrophy in type II muscle fibers (19). Muscle loss is more marked after the age of 70 years (18). In a study by Evans et al. (20), they suggested that 50% of muscle mass will be lost between the age of 45 years and 90 years if no specific preventive measures have been considered. Hughes et al. (21) reported that the annual muscle mass loss was 1%-2% after 50 years of age.

It is assumed that sarcopenia is a result of hormonal and immunological alterations that occur on account of aging. There is conflicting information regarding the impact of estrogens on sarcopenia. Epidemiologic and interventional studies suggest that due to decrease in estrogen by time that results increase in levels of pro-inflammatory cytokines such as TNF- α and IL-6, estrogen that is thought to be responsible for sarcopenia process protect from muscle mass loss (22). Cytokines, particularly TNF- α and IL-6, are believed to increase muscle loss (6).

Aging, however, is associated with a chronic, gradual increase in the production of pro-inflammatory cytokines, mainly IL-6 and IL-1. There is evidence suggesting that an increase in adipose tissues with a reduction in circulating sex hormone levels with age contributes to this increase in pro-inflammatory cytokines, which elevates the catabolic stimulus. Thus, aging itself is associated with an elevated catabolic stimulus; however, there is no prospective evidence that cytokines could be predictors of sarcopenia. Nevertheless, sarcopenia is one of the consequences of cytokine-related aging (23).

Previous studies in older populations have suggested that there is an association between sarcopenia and high IL-6 levels (4). In a study by Visser et al. (24), it was reported that there

Table 3. Comparison of SMI between the groups

Groups	SMI (mean \pm SD)
RA	5.83 \pm 0.80
Control	7.30 \pm 1.64
Outcome	t=4.40, p=0.022, p<0.05

SMI: skeletal muscle index; RA: rheumatoid arthritis

Table 4. Sarcopenia distribution in the groups ($\chi^2=8.52$, $p=0.004$; $p<0.05$ significant)

Groups	Sarcopenia		Total
	+	-	
RA, n (%)	13 (43.3)	17 (56.7)	30
Control, n (%)	3 (10.0)	27 (90.0)	30
Total, n (%)	16 (26.7)	44 (73.3)	60

RA: rheumatoid arthritis

Table 5. Relationship between sarcopenia and BMI in the groups ($\chi^2=15.13$; $p=0.001$ and $p<0.05$ significant)

Groups	BMI			Total	
	Normal 18.5-24.9	Overweight 25-29.9	Obese 30-39.9		
RA (+) Sarcopenia	n (%)	6 (46.2)	6 (46.2)	1 (7.6)	13
RA (-) Sarcopenia	n (%)	0 (0.0)	5 (29.4)	12 (70.6)	17
Total	n (%)	6 (20.7)	11 (36.7)	13 (43.3)	30

BMI: body mass index; RA: rheumatoid arthritis

Table 6. CRP distribution in relation to sarcopenia status in the RA group ($p=0.023$; $p<0.05$ significant)

Groups	CRP		Total
	Normal <8 mg/L	High ≥ 8 mg/L	
RA sarcopenia +	n	5	13
	%	38.5	100
RA sarcopenia -	n	14	17
	%	82.4	100
Total	n	19	30
	%	63.3	100

CRP: C-reactive protein; RA: rheumatoid arthritis

is an association between muscle strength and mass measurements and blood TNF- α , IL-6, and CRP levels. In the Longitudinal Aging Study Amsterdam, it was reported that high levels of IL-6 and CRP are related to loss in muscle strength. These cytokines increase proteolysis during muscle tissue synthesis. Schaap et al. (25) found an association between high CRP levels and sarcopenia. Cesari et al. (26) found a relationship between high CRP levels and sarcopenia in a study that was conducted in 286 subjects (mean age: 66 years) with cardiovascular disease.

Recent studies have revealed that chronic inflammatory diseases lead to sarcopenia (7). It is believed that the inflammatory cytokines TNF- α and IL-1 β have pivotal roles in RA pathogenesis. Given that TNF- α is elevated in RA, one could propose that RA may cause and accelerate the course of sarcopenia (7). In patients with RA, a decrease in physical activity (8), elevated TNF- α and IL-1 β levels, increased energy expenditure during rest, high CRP levels, immobility secondary to stiffness, and pain increase the risk of sarcopenia (9).

Munro et al. (27) evaluated BMI, lean body mass, and acute phase reactants in 97 patients with RA and found a negative correlation between muscle mass and CRP levels and ESR in female patients with RA. In the present study, when we evaluated sarcopenia status and CRP levels, we found that CRP levels were high in RA patients with sarcopenia.

Westhovens et al. (28) evaluated BC in 89 patients with RA (43 males and 46 females) and 157 controls and found that lean body mass was significantly lower in the RA group. In the present study, SMI was found to be significantly low.

The study by Giles et al. (29) was the first and largest to evaluate BC and the relationship be-

tween abnormal BC phenotypes and RA characteristics in patients with RA. They observed that among female patients with RA, high fat mass and low lean body mass was more prominent in women with a normal body weight. They found that such alterations in BC were associated with RF positivity, CRP levels, joint deformity, and health assessment questionnaire (HAQ) scores but not with the DAS28 score. In our study, we did not find any significant relationship between the DAS28 score and sarcopenia, although CRP levels were high in RA patients with sarcopenia. This can be explained by the fact that most of our patients with RA were in remission or had mild disease activity according to the DAS28 score. This discrepancy appears to be reasonable, because CRP is only one of the parameters that were used in DAS28 calculation.

Giles et al. (29) evaluated BC and found that sarcopenia frequency was significantly higher in the RA group than in the control group and sarcopenia was more common in the normal BMI subset of the RA group. Dao et al. (30) evaluated BC in women with early RA and found that sarcopenia frequency was significantly higher in the early RA group and these BC changes were associated with RF seropositivity and HAQ and DAS28 scores. In the study by Santos et al. (31), abnormal BC was more frequent in women with SLE and RA than in non-inflammatory controls despite having a similar BMI. In the present study also, we found that sarcopenia was more frequent in the RA group than in controls and more common in the normal and overweight subset than in the obese subset according to BMI.

TNF- α leads to atrophy in muscle tissue in vitro. TNF- α that is used in RA treatment could be an alternative treatment option for sarcopenia (32). Metsios et al. (33) who evaluated BC, ESR, CRP levels, and DAS28 scores before and

after 12-week anti-TNF therapy showed that no significant change occurred, whereas marked improvement was achieved in disease activity with this treatment in 20 patients with RA.

According to Giles et al. (29), subjects who are receiving DMARDs have a lesser tendency to exhibit abnormal BC. Glucocorticoids, however, have no relationship with abnormal BC. Although the accumulative effects of RA appear to be related to abnormal BC, it has been suggested that it develops in early course of disease, as no protective effect of RA against abnormal BC have not found yet. It is expected that biological agents reduce the catabolic effects of hypercytokinemia in muscle by their anti-inflammatory action.

In their cross-sectional analysis, Giles et al. (29) reported that DMARD treatment alone, biologic or not, is associated with a reduction in the risk of abnormal BC. In our study, no association was found between steroid, DMARD, and biological agent use and sarcopenia development. This may be due to the cross-sectional analysis that we employed to assess drug use.

Our study had some limitations. We did not assess muscle performance in our study. Furthermore, in our study, only female patients with RA were enrolled. Sarcopenia in male patients with RA was not examined. Also the number of patients was small. This is another limitation of our study.

In conclusion, our study showed that SMI values are low and there is an increase in sarcopenia risk in patients with RA. Sarcopenia risk is lower in obese RA patients than in normal or overweight RA patients. Further studies are needed for better understanding of sarcopenia to clarify the role of sarcopenia in RA and to evolve therapeutic strategies.

Ethics Committee Approval: Ethics committee approval was received for this study from the Local Research Ethics Committee.

Informed Consent: Informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.H.; Design - S.C.D.; Supervision - S.H.; Materials - S.C.D.; Data Collection and/or Processing - S.C.D., E.H., E.G., T.E.; Analysis and/or Interpretation - E.K., T.E.; Literature Review - S.C.D.; Writer - S.C.D.; Critical Review - S.C.D., S.H.

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